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Original Research

Is only Thyroid Peroxidase Antibody Sufficient for Diagnosing Chronic Lymphocytic Thyroiditis?

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Abstract

Objectives: Recently, only anti-thyroid peroxidase (anti-TPO) has been suggested as an autoantibody in the diagnosis of chronic lymphocytic thyroiditis (CLT). In contrast, anti-thyroglobulin (anti-Tg) positivity has also been reported to be important. To evaluate this relationship more clearly, we planned to retrospectively investigate the autoantibody levels of the patients who underwent thyroid surgery for various reasons and those with CLT in postoperative pathology.

Methods: We evaluated 670 patients who underwent thyroid surgery (total/subtotal thyroidectomy) for various reasons at our hospital between January 2015 and March 2017. Patients with indications of Graves' disease, toxic multinodular goiter, and all malignancies except for thyroid papillary carcinoma (TPC) were excluded. Eighty-nine patients whose pathology findings were compatible with CLT and preoperative thyroid autoantibodies were identified enrolled in to the study. Patients with absence and presence of thyroid antibodies were included in the seronegative CLT group and seropositive CLT group, respectively. In addition, patients were divided into thyroid papillary carcinoma (TPC) and benign groups.

Results: According to the study criteria, 89 (83 females, six males) (mean age, 46.08±11.19 years) patients who had preoperatively identified autoantibodies were detected. Anti-TPO positivity was found in 47 (52.8%) cases, whereas anti-Tg positivity was found in 49 (55.1%). Only anti-TPO positivity was found in 18 (20.2%) cases, whereas only anti-Tg positivity was detected in 20 (22.5%). Twenty-two (24.7%) of the patients were seronegative. On comparing the seronegative and seropositive groups, seronegativity was more frequent in male patients (p=0.03). Thyroid-stimulating hormone was found to be significantly higher in the seropositive group (p=0.01). TPC was detected in 36 (40.4%) of all cases. No difference regarding age, thyroid function tests, and antibody levels was found between the benign and TPC groups.

Conclusion: Although all of our cases were histopathologically diagnosed with CLT, serologically, 75.3% of thyroid autoimmunities could be shown when both antibodies were evaluated together. When only anti-TPO was considered, this rate decreased to 52.8%. Therefore, anti-Tg appears to be still important in showing autoimmunity. Prospective studies are needed to evaluate this relationship more clearly.

Keywords: Autoantibodies; chronic lymphocytic thyroiditis; pathology.

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In the general population, chronic autoimmune thyroiditis has been detected as the most frequent cause of hypothyroidism. Hashimoto thyroiditis, chronic autoimmune thyroiditis, and chronic lymphocytic thyroiditis (CLT) are interchangeably used to define the same disease.[1] CLT occurs because of the impairment of self-tolerance against thyroid autoantigens, and autoantibodies formed against thyroid antigens are detected in the blood samples of CLT. These autoantibodies formed against thyroid peroxidase and thyroglobulins are considered to be the main markers of this autoimmune thyroid disease.[1, 2]

It is debatable as to what extent anti-thyroglobulin (anti-Tg) antibodies formed against thyroglobulin represent autoimmunity.[3-5] A laboratory guideline for thyroid diseases formed in 2003 states that investigating anti-Tg is not recommended for detecting autoimmune thyroid diseases where iodine intake is sufficient.[3] As reported in the Turkish Society of Endocrinology, and Metabolism 2017 guideline, anti-thyroid peroxidase (anti-TPO) positivity was detected in 95% of the cases with CLT, and isolated anti-Tg positivity was observed in 5%.[6] However, some studies have reported higher rates of anti-Tg positivity. In a study from our country evaluating the incidence of thyroid autoantibody, isolated anti-Tg positivity was detected in 22.41% of the cases.[7]

The incidence rates of the thyroid autoantibody may vary among populations and age groups. Though its prevalence in the general population varies considerably, it is more frequently seen in women. The incidence of the CLT disease may increase up to 12%–15% in 30–40-year-old women.[4, 8] Thyroid autoantibodies are polyclonal[9], and they are generally immunoglobulin (Ig) G1 or IgG3 antibodies; however, they may belong to any subclass. Therefore, their complement fixation characteristics and abilities to pass through the placenta may change. Some Tg and TPO antibodies may fragment thyroid cells in in vitro settings and inhibit the enzymatic activity of TPO.[10, 11] However, these types of observational information are debatable.[12] The polyclonal nature of these autoantibodies demonstrates that they are formed secondary to thyroid damage initially caused by T cells. Preliminary studies supported the hypothesis suggesting the pathogenic role of TPO antibodies in the development of autoimmune thyroiditis.[13]

Babies born to TPO antibody-positive mothers have normal thyroid glands,[14] which raises the possibility of TPO antibodies being a marker and/or a risk factor rather than its pathogenic role.[15] However, some studies have indicated the presence of a stronger correlation between histopathological findings and anti-Tg.[16]

Since several literature studies have detected anti-Tg positivity,[7, 17] we planned to retrospectively investigate patient's serum thyroid autoantibody status who had postoperative histopathological specimens compatible with CLT.

Methods

This is a retrospective, hospital-based study. We evaluated 670 patients who underwent thyroid surgery (total/subtotal thyroidectomy) for various reasons at our hospital between January 2015 and March 2017. Patients with indications of Graves' disease, toxic multinodular goiter, and all malignancies except for thyroid papillary carcinoma (TPC) were excluded. Eighty-nine patients whose pathology findings were compatible with CLT and preoperative thyroid autoantibodies were identified enrolled in to the study. Patients' demographic, ultrasonographic, and histopathological characteristics were investigated. Ethics committee approval was obtained for our study.

Anti-TPO, anti-Tg, fT3, fT4, and thyroid-stimulating hormone (TSH) were analyzed using the electrochemiluminescence immunoassay method (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). TSH 0.005 μIU/mL was measured with analytical sensitivity . The ranges of measurements for anti-Tg and anti-TPO were 10–4000 IU/mL & 5–600 IU/mL, respectively. Anti-Tg and anti-TPO were considered as negative for values below 115 IU/mL and 35 IU/mL, respectively.

CLT were defined as atrophic changes including diffuse/focal lymphoplasmacytic infiltrates, oxidative cells, germinal centered lymphoid follicles. In cases diagnosed as TPC, lymphocytic infiltration only into the tumor or its periphery was not defined as CLT, and these cases were excluded.

Statistical Analysis

Data were expressed as mean±standard deviation. Among numerical data, parametric data with normal distribution were evaluated using Student t test and those with non-normal distribution were evaluated using Mann–Whitney U test. Categorical variables were evaluated using chi-square test and Fischer's exact test. The relationship between non-parametric data was evaluated using Spearman correlation analysis. SPSS 21.0 (SPSS Inc, IL, USA) program was used for calculations. $P<0.05$ was accepted as the level of statistical significance.

Results

A total of 89 surgically treated patients (mean age, 46.08±11.19 years; 83 female and six male) with various indications, histopathologically diagnosed with lymptocytic thyroiditis who had preoperatively investigated thyroid autoantiboides were identified. Anti-TPO positivity (n=47; 52.8%) and anti-Tg positivity (n=49; 55.1%) were detected in respective number (%) of cases. In contrast, solely anti-TPO (n=18; 20.2%) and anti-Tg (n=20; 22.5%) positivities were detected in the indicated number of patients (Table

1). In 22 (24.7%) patients, anti-TPO and/or anti-Tg negativities were found. This group was termed as the seronegative CLT group. Cases having at least one of the thyroid antibodies were included in the seropositive group. Seronegative and seropositive groups were compared, and seronegativity was more frequently seen among male patients (p=0.03) (Table 2). The TSH levels were significantly higher in the seropositive group (p=0.01). A significant correlation was not detected in the correlation analysis of anti-TPO and anti-Tg levels. Any intergroup difference was not seen regarding the presence of malignancy.

Table 1. Distribution of frequencies of antibodies in our cases

	Anti-Tg (–) n (%)	Anti-Tg (+) n (%)	Total n (%)
Anti-TPO (–)	22 (24.7)	20 (22.5)	42 (47.2)
Anti-TPO (+)	18 (20.2)	29 (32.6)	47 (52.8)
Total	40 (44.9)	49 (55.1)	89 (100)

(p=0.2).

In 40.4% (n=36) of all cases, TPC was detected. Of the 36 TPC cases, 21 (58.3%) had papillary microcarcinoma and the remaining 15 (41.7%) had papillary carcinomas larger than 1 cm in diameter. Lymph node metastasis was detected in five (13.9%) cases. Multicentricity was found in 19 (52.8%) malignant cases. Any significant difference between cases with the histopathological diagnoses of TPC and benign group was not observed with respect to age, thyroid function test results, and antibody levels (Table 3).

Table 2. Comparison of seronegative and seropositive groups (seronegative group : anti-TPO and anti-Tg negative; Seropositive group: anti-TPO and/or anti-Tg positive)

	Seronegative group (n=22)				Seropositive group (n=67)				p
	Mean	Standard deviation	Median	Min-Max	Mean	Standard deviation	Median	Min-Max	
Age (year)	46.09	13.20	43	28-72	46.07	10.57	47	19-72	0.9*
Free T3(pg/mL)	3.41	0.55	3.26	2.71-4.55	3.09	0.44	3.17	1.72-3.9	0.07*
Free T4 (ng/dL)	1.21	0.16	1.25	0.88-1.46	1.21	0.29	1.17	0.69-2.62	0.9*
TSH (µIU/mL)	1.99	1.16	1.96	0.39-4.25	3.05	1.76	2.82	0.65-9.65	0.01†
Anti-TPO (IU/ml)	13.28	7.37	11.23	5-30.53	165.27	160.78	125	5-517	0.01†
Anti-Tg (IU/ml)	35.66	25.93	30.05	10.45-109.2	269.22	178.78	267.5	12.6-546	0.01†
Sex (female/male)	18/4				65/2				0.03‡
Malignancy (yes/no)	9/13				27/40				0.57‡

*Student T Test, †Mann–Whitney U Test, ‡Chi-square Test.

Table 3. Comparison between groups with thyroid papillary carcinoma and benign histopathology

	Benign (n=53)				Thyroid Papillary Carcinoma (n=36)				p
	Mean	Standard deviation	Median	Min-Max	Mean	Standard deviation	Median	Min-Max	
Age (years)	47.91	11.21	47	21-72	43.39	10.77	45	19-72	0.06*
Free T3(pg/mL)	3.18	0.54	3.17	1.72-4.55	3.16	0.41	3.16	2.4-4.07	0.8*
Free T4 (ng/dL)	1.22	0.31	1.21	0.69-2.62	1.20	0.18	1.19	0.88-1.58	0.6*
TSH (µIU/mL)	2.57	1.55	2.35	0.39-9.65	3.10	1.84	3.03	0.52-7.09	0.08†
Anti-TPO (IU/ml)	145.74	172.97	45.82	5-517	101.15	118.50	34.49	5-430.2	0.07†
Anti-Tg (IU/ml)	209.52	190.00	147.1	11.89-546	214.37	181.22	193.75	10.55-545	0.9†
Sex (f/m)	51/2				32/4				0.17‡
Anti-TPO (positive/negative)	29/24				18/18				0.41‡
Anti-Tg (positive/negative)	28/25				21/15				0.38‡
Seropositive/ Seronegative group	40/13				27/9				0.57‡

*Student T Test, †Mann–Whitney U Test, ‡Chi-square Test.

Discussion

In our study, although all our cases were histopathologically diagnosed with CLT, in approximately one of four patients, both anti-Tg and anti-TPO negativities were detected. Histologically detection rate of Hashimoto thyroiditis is much higher than that of CLT diagnosed on the basis of serologic tests.[18] Despite the availability of highly sensitive measurement methods, in some patients with hypothyroidism, these antibodies cannot be detected.[19] Since hypoechoic thyroid pattern is observed in most of these patients during ultrasonographic examination, they have been considered to have seronegative autoimmune thyroiditis (SN-AIT).[20] In population-based studies, the prevalence of SN-AIT has been estimated to be 5%.[19] Nowadays, owing to ultrasensitive TSH measurement methods, a higher number of subclinical hypothyroidism cases are being diagnosed. Therefore, the detection of higher number of seronegative cases is anticipated.[8, 21] Only limited number of studies have investigated the clinical course of SN-AIT.

In our study, isolated anti-Tg elevation was detected in 20% of the cases. In population-based studies, its incidence is indicated as 5%. Histopathological findings and anti-Tg demonstrate a stronger correlation.[16] Anti-Tg prevalence may reportedly increase with age in healthy groups without thyroid disease. However, in an autopsy study performed with cadavers of old patients without any history of thyroid disease, an increase in lymphocytic infiltration together with anti-Tg positivity was demonstrated.[16] In the follow-up of the patients with TPC who underwent surgery, thyroglobulin was investigated; however, the importance of anti-Tg measurement is also known. The clinical usefulness of measuring serum anti-Tg levels to demonstrate thyroid autoimmunity has been debated in recent years. In a NHANES III study performed in the USA, isolated anti-Tg positivity was detected in 3% of the patients with anti-TPO negativity, and anti-Tg positivity was not indicated as a risk factor for the development of thyroid disease.[4] After this study in patients with higher TSH levels living in regions with adequate environmental iodine, anti-Tg was not suggested to be a helpful biomarker to demonstrate autoimmune thyroid disease.[5, 22] However, authors stated that this suggestion did not hold true for environmental iodine-deficient regions. In iodine-deficient regions, especially in patients with nodular goiter, the benefit of anti-Tg measurements in the demonstration of autoimmunity has been indicated.[3] Our country is still described as a region of moderately severe iodine deficiency. After iodization of table salts, this problem seems to be resolved in the city centers; however, in the rural areas, this problem still prevails.[6] In addition to anti-Tg positivity, its avidity also conveys importance. It has been demonstrated that in the follow-up of the anti-Tg positive cases with euthyroidism and patients with subclinical and manifest hypothyroidism, those with higher anti-Tg avidity progressed to hypothyroidism more frequently.[23]

In our study, any relationship between antibody titers and TPC was not observed. The relationship between CLT and papillary thyroid carcinoma is a debatable issue. In some studies, a correlation was demonstrated, while in some other studies no correlation could be detected.[24] In studies on thyroidectomy, a positive correlation was detected between malignancy and CLT, while in population-based studies performed using fine-needle aspiration biopsy, a significant correlation could not be found. Chronic inflammation has been indicated as a potential etiologic agent in malignant transformation developed in epithelial cells;[25] on the contrary, some publications have indicated that lymphocytic infiltration induces an immunological response, which delays tumorigenesis, exerts a potential protective effect, and contributes favorably to prognosis.[24, 26-28]

The preoperative antibody levels of many patients have not been measured at our center. Therefore, the number of patients included in the study was much less than the operated patients, which was the main factor limiting our number of cases. Another limitation of the study stemmed from its retrospective design. Further prospective studies should be performed to be able to evaluate this correlation more clearly.

Currently, the number of cases with subclinical hypothyroidism is gradually increasing, and antibody positivity and its levels may be a guiding tool in the selection of candidate patients requiring treatment.[29, 30] Since a gradual increase in the number of seronegative patients is anticipated, physicians may become hesitant in prescribing treatment to some patients. In our study, the positivity of both antibodies was seen at similar rates. When both antibodies were evaluated in combination, serologically, thyroid autoimmunity could be demonstrated in 75.3% of cases. When only a single antibody was investigated, the rate of thyroid immunity decreased to 50%. In these groups, when only anti-TPO is investigated to demonstrate autoimmunity, approximately 25% of the cases with CLT may be overlooked. When this condition is considered, we think that anti-Tg retains its importance in the demonstration of autoimmunity.

Disclosures

Ethics Committee Approval: The study was approved by the

Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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